Remarks

Claims 1-40 are currently pending in the application. Claims 1-3, 5, 8-14, 16, 18, 22, 23 and 37 are currently amended. Claims 15, 19-21, 24-36, 39 and 40 are canceled without prejudice as drawn to non-elected subject matter. Additionally, claims 6 and 7 are canceled herein. New claims 41 and 42 are added. Applicant expressly reserves the right to prosecute the subject matter of canceled claims 6 and 7 in this or a related application. Support for new claims 41 and 42 is found in the specification at least in the Examples and in the sequence listing. Upon entry of the present amendments, claims 1-5, 8-14, 16-18, 22, 23, 37, 38, 41 and 42 will be pending in this application.

Claims 1, 2, 9, 14, 16, 18, 22, 23 and 37 are amended to delete recitation of "substantial functional equivalent". Support for these amendments may be found in the specification and in the claims as originally filed. More specifically, claim 5 is amended to replace recitation of "codes for" with the more accurate "comprises." Claim 14 is amended to recite that the hybridizing nucleic acid comprises portions hybridizing to the 3′ and to the 5′ side of the apo-dystrophin-4 inversion start. Support for the amendment to claim 14 is found at least on page 18, lines 9-28, and page 19, lines 4-18. Claim 18 is amended to recite the claimed polynucleotides in the alternative rather than as members of a Markush group. Claim 18 is also amended to recite that the recited polynucleotide in the claimed cell is inverted with respect to the native dystrophin sequence. Support for the latter amendment to claim 18 is found at least at page 23, lines 9-10, and the sequences of SEQ ID NO: 1 and SEQ ID NO: 2.

It is submitted that no new matter has been introduced by the present amendments and new claims and entry of the same is respectfully requested. By the amendments, Applicant does not acquiesce to the propriety of any of the Examiner's rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (1997).

The Rejections of Claims 1-14, 16-18, 22-23 and 37-38 Under 35 U.S.C. § 112, First Paragraph, Lack of Written Description, Should be Withdrawn

The Examiner has rejected claims 1-14, 16-18, 22-23 and 37-38 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the specification discloses only a single variant of SEQ ID NO: 2 containing the polynucleotides of SEQ ID NO: 1 or variant thereof, and that this disclosure is not sufficient to support claims directed to SEQ ID NOS: 1 or 2, and variants thereof. Applicant traverses.

Without conceding the correctness of the Examiner's contentions, Applicant has amended claims 1, 2, 5, 9, 14, 16, 18, 22 and 23 to delete recitation of "substantial functional equivalent". Applicant expressly reserves the right to prosecute the subject matter of the unamended claims in this or a related application. As amended, the scope of these claims is commensurate with the specification's disclosure of SEQ ID NO: 2, SEQ ID NO: 1, and variants of SEQ ID NO: 1 comprising an additional 10-150 nucleotides immediately upstream of the 5′ end of SEQ ID NO: 1 (*see*, for example, the sequences of SEQ ID NOS: 1A and 1B), as is the scope of the claims dependent from these claims.

With respect to claims 6 and 7, Applicant has canceled these claims, mooting the Examiner's rejection of them on this basis. With respect to claim 8, Applicant submits that it is evident from the nucleotide sequence of SEQ ID NO: 1 that it codes for a plurality of stop codons (*see* FIG. 1); thus, in combination with the above-referenced amendments, claim 8 enjoys adequate support in the specification.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of 1-14, 16-18, 22-23 and 37-38 on this basis.

The Rejections of Claims 1-14, 16-18, 22-23 and 37-38 Under 35 U.S.C. § 112, First Paragraph, Lack of Enablement, Should be Withdrawn

The Examiner has rejected claims 1-14, 16-18, 22-23 and 37-38 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the number of polynucleotide sequence variants allegedly encompassed by the claims would encode a large number of variants of apo-dystrophin-4, and that it would "require an undue amount of experimentation to characterize every possible variant for the claimed functional activity (*i.e.*, binding to CD33 and modulation of CD33 mediated signal transduction). Applicant traverses.

Without conceding the correctness of the Examiner's contentions, Applicant has amended claims 1, 2, 5, 9, 14, 16, 18, 22 and 23 to delete recitation of "substantial functional equivalent". Applicant expressly reserves the right to prosecute the subject matter of the unamended claims in this or a related application. As amended, the scope of these claims is commensurate with the specification's disclosure of SEQ ID NO: 2, SEQ ISD NO: 1, and variants of SEQ Id NO: 1 comprising an additional 10-150 nucleotides immediately upstream of the 5′ end of SEQ ID NO: 1 (*see*, for example, the sequences of SEQ ID NOS: 1A and 1B), as is the scope of the claims dependent from these claims.

As amended, the claims are enabled. Persons of skill in the art are provided with nucleic acid sequences encoding apo-dystrophin-4, and regulating the expression thereof

(*e.g.*, SEQ ID NO: 2, SEQ ID NO: 1, and variants of SEQ ID NO: 1 comprising an additional 10-150 nucleotides immediately upstream of the 5′ end of SEQ ID NO: 1 (*see*, for example, the sequences of SEQ ID NOS: 1A and 1B). Persons of skill in the art are also provided methods of expressing these sequences, and of determining whether apo-dystrophin-4 variants are expressed (*e.g.*, through use of anti-apo-4 antisera) and whether these variants are able to bind CD33 (*e.g.*, through use of Fc-CD33). Such experiments, once one has the disclosed nucleic acid sequences in hand, are routine to perform. A substantial amount of experimentation is not a bar to enablement where the experimentation is routine, such as the expression of nucleic acids and the generation and use of antibodies (*see In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)).

The Examiner appears to believe that the sequence of apo-dystrophin-4 is the result of alternative splicing (*see*, *e.g.*, Office Action at page 8, first paragraph, and page 9, second paragraph). This is not the case; the best explanation for the structure of apo-dystrohpin-4 is a genetic rearrangement, such as that caused by a transposon. *See* specification at page 84, lines 26-27, and accompanying text. Applicant notes that the Sironi paper, which the Examiner cites as evidence that alternative splicing may be a disease determinant (Sironi *et* al., *FEBS* Lett. 517:163-166 (2002); see Office Action, page 8), was published after the earliest priority date to which Applicant is entitled. As such, it does not represent the state of the art at the time of Applicant's filing, and should not be used as evidence of nonenablement.

With respect to claims 17 and 18, the Examiner contends that claims 17 and 18 read on cells created by gene therapy, and transgenic animals, and that these are not enabled by the specification. Applicant traverses. At the time of filing, the delivery and expression of nucleic acid sequences into, for example, muscle tissue, was well-known. *See*, *e.g.* Walter *et al.*, "Noninvasive Measurement of Gene Expression in Skeletal Muscle," *Proc. Natl. Acad. Sci. U.S.A.* 97(10):5151-5155 (2000), a copy of which is attached hereto; *see also* Wolff *et al.*, "Direct Gene Transfer Into Mouse Muscle *in Vivo*," *Science* 23:247(4949 Pt 1):1465-8 (1990). Thus, making a host cell produce recombinant protein, *in vivo*, wherein the host cells are created by a method of gene therapy is, in fact, routine in the art, particularly in muscle, the context in which the sequences of the present invention would be particularly useful.

The Examiner cites Rosenberg, *Science* 287:1751 (2000) in support for the position that gene therapy "has fallen short of initial expectations." Office Action at page 10. The Rosenberg article is merely the expressed opinion of a single individual, and does not represent the state of the art of gene therapy; Rosenberg does not, for example, support his

view with any scientific evidence. Rosenberg also does not credit successes in the expression of exogenous sequences in mouse muscle models, as described in the papers cited above.[1]

Applicant therefore maintains that claims 17 and 18 are enabled by the specification, and respectfully request that the Examiner withdraw the rejection of these claims on this basis.

With respect to claims directed to regulatory elements, the Examiner does not take into account experimental evidence that the disclosed sequences do, in fact, act as a regulatory element. The Examiner states that "the specification as filed fails to disclose and [*sic*] that polynucleotides of SEQ ID NO:1 or SEQ ID NO:2 contains a promoter or any transcriptional factor binding sites which is [*sic*] capable of regulating the expression of a gene or other DNA sequences to which it is operatively linked." Office Action at page 10. In fact, Applicant has shown that the nucleotide sequence of the polynucleotide of claim 9 is necessary for the expression of the proteins expressible from SEQ ID NO: 2. *See* page 87, line 18 to page 88, line 27. This facilitation of expression by the polynucleotide of claim 9 results from the suppression of stop codons in the sequence to which the polynucleotide of claim 9 is operatively linked. *Id.* Thus, the nucleotide sequence of the polynucleotide of claim 9 is a regulatory sequence in that it controls the expression of an operably linked nucleotide sequence. Applicant has therefore provided the nucleotide sequence of the polynucleotide of claim 9 (*i.e.*, its structure), and has correlated that structure with its function (*i.e.*, enabling readthrough of stop codons). Thus, the Examiner's statement that "[t]he specification fails to provide a single working example which establishes that polynucleotides of SEQ ID NO: 1 or SEQ ID NO: 2 are capable of regulating the expression of a gene or a DNA sequence to which it is operatively linked" (Office Action, page 10) is incorrect. Applicant need not have explored or described whether the polynucleotide of claim 9 contained any transcription factor sites or a promoter. Any experimentation required to use the polynucleotide of claim 9 to control expression of a nucleotide sequence involves only routine cloning and expression analysis, and thus is not undue.

The Examiner further rejects claims 37 and 38 because of, *inter alia*, the unpredictability in the treatment of leukemia. Office Action at page 11.[2] Applicant traverses.

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[1] *See also* Sweeney, *Scientific American* 291(1):62-69 (2004) (attached hereto; published after the present application's filing date but addressing experiments performed prior to the filing date), discussing gene therapy, *inter alia*, in the context of muscle tissue.

[2] The Examiner also states that the specification teaches that the "regulation of CD33 including those elements to which it binds *in vivo*, is not fully understood and there is a need for investigation of this biological system," citing page 1, lines 17-20. Page 1, lines 17-20 do not stand for this proposition; the Examiner is requested to clarify.

The specification also teaches that the nucleotide sequences of the invention may be used to treat conditions resulting from protein truncation. Page 22, lines 4-15. The formulation of nucleic acids into pharmaceutically-acceptable compositions is known. The delivery and expression of nucleic acid sequences into, for example, muscle tissue, is known. *See, e.g.* Walter *et al.*, "Noninvasive Measurement of Gene Expression in Skeletal Muscle," *Proc. Natl. Acad. Sci. U.S.A.* 97(10):5151-5155 (2000), a copy of which is attached hereto; *see also* Wolff *et al.*, "Direct Gene Transfer Into Mouse Muscle *in Vivo*," *Science* 23:247(4949 Pt 1):1465-8 (1990). Such an expressed nucleic acid may be, the specification teaches, an antisense nucleic acid. Page 23, first paragraph. Moreover, Applicant has amended claims 37 and 38 to recite that it is a polynucleotide of SEQ ID NO: 1, or a polynucleotide of claim 1, that is administered. As such, Applicant submits that claims 37 and 38 are enabled.

The claims as amended, therefore, are fully enabled by the specification. Applicant therefore respectfully requests that the Examiner withdraw the rejection of 1-14, 16-18, 22-23 and 37-38 on this basis.

The Rejection of Claims 1-14, 16-18, 22-23 and 37-38
Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

The Examiner has rejected claims 1-14, 16-18, 22-23 and 37-38 under 35 U.S.C. § 112, second paragraph as indefinite in the recitation of "substantial functional equivalent." Office Action at page 13. Without conceding the correctness of the Examiner's rejection, Applicant has, as noted above, amended the relevant claims to delete recitation of "substantial functional equivalent." Applicant requests that the Examiner withdraw the rejection of the claims on this basis.

The Examiner has also rejected claims 16 and 17 as indefinite in their recitation of "a transcription promoter operably linked to a selection from the group consisting of." Office Action at page 13. Applicant has amended claim 16 to recite the claimed polynucleotides in the alternative, rather than in Markush form, thus obviating the Examiner's rejection. Applicant respectfully requests that the Examiner withdraw the rejection of claim 16, and 17, which depends from claim 16, on this basis.

The Examiner has also rejected claim 18 as indefinite in its recitation of "a cell comprising a selection from the group consisting of." Office Action at page 13. Applicant has amended claim 18 to recite the claimed cell in the alternative, rather than in Markush form, thus obviating the Examiner's rejection. Applicant respectfully requests that the Examiner withdraw the rejection of claim 18 on this basis.

The Rejection of Claims 14 and 16-18 Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Examiner has rejected claim 14 under 35 U.S.C. § 102(b) as anticipated by Hillier *et al.*, Accession Nos. H27701 and H89576. Office Action, page 14. The Examiner contends that these two nucleotide sequence accession pages disclose nucleotide sequences that hybridize to the sequence shown in SEQ ID NO: 2 or SEQ ID NO: 1, respectively. Without conceding the correctness of the Examiner's rejection, Applicant has amended claim 14 to recite that the hybridizing nucleic acid comprises portions hybridizing to the 3′ and to the 5′ side of the apo-dystrophin-4 inversion start. Neither of the references cited by the Examiner disclose the junction between normal dystrophin sequence and the inversion sequence, as shown in the apo-dystrophin-4 sequence of, for example, SEQ ID NO: 2. As such, neither Hillier reference anticipates claim 14 as amended. Applicant respectfully requests that the Examiner withdraw the rejection of claim 14 on this basis.

The Examiner has also rejected claims 16-18 under 35 U.S.C. § 102(b) as anticipated by Hillier *et al.* H89576. Office Action, page 14. The Examiner contends that Hillier shows a cDNA sequence from a human dystrophin gene, matching SEQ ID NO: 1, and teaches "the cloning of polynucleotide sequences of SEQ ID NO: 1 in the pBluescript SK– expression vector and kanamycin resistance SOLR host cells . . . ." Office Action, page 15. Applicant traverses.

Hillier does not teach all elements of claim 16, upon which claim 17 depends, or of claim 18, as amended. Claim 16 requires that the nucleotide sequence of SEQ ID NO: 1, when present in the recited vector, is inverted relative to normal human dystrophin; that is, the sequence is reversed. Likewise, claim 18 requires that the nucleotide sequence of SEQ ID NO: 1 be inverted relative to normal human dystrophin. Hillier does not show the disclosed sequence in such an inverted orientation. Hillier thus does not anticipate claim 16 or 18 as amended; because Hillier does not anticipate claim 16, it also does not anticipate claim 17, which depends from claim 16. Applicant requests that the Examiner withdraw the rejection of claims 16-18 on this basis.

CONCLUSION

Applicant respectfully requests that the above amendments and remarks be entered in the present application file. An early allowance of the present application is respectfully requested.

No fee is believed due for this Amendment. However, if a fee is due, please charge such fee to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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